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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,736	01/06/2004	Robert Vincent Martinez	WYE-031	2977

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EXAMINER	
YAO, LEI	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,736	MARTINEZ ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/10/07*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

The request filed 1/7/07 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10751736 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 3, 4 and 8-20 have been cancelled. It is noted that claim 7, as original filed and amended, does not recite either the method comprising detecting mRNA or polypeptide expression in the claim. However, applicant originally elected group 17, a method for detecting a level of polypeptide encoded by colon cancer gene, GPR49 (SEQ ID NO: 84) for examination. In the previous prosecution, together with claims 1-6, the method of claim 7 has been examined comprising a step of detecting the levels of polypeptides, not mRNA, of GPR49, in colon samples. In this office action, claims 1, 2, and 5-7 are still pending and are continually examined for a method of diagnosing colon cancer comprising the step of detecting and comparing the levels of GPR49 polypeptide in colon cancer sample.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 1/10/07 is/are considered by the examiner and initialed copy/copies of the PTO-1449 is/are enclosed.

Claim Rejections - 35 USC § 101/112 first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, and 5-7 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility.

Claims are drawn to a method of diagnosing or monitoring colon cancer in a subject comprising the steps of detecting and comparing over expressed level of a GPR49 polypeptide or expression profile comprising CPR49 polypeptide in biological samples of a subject.

The specification teaches that 495 genes were found two fold expression in cancer tissues and 63 genes are over expressed in colon cancer tissues compared to normal colon tissues determined by microarray (RNA levels, para 433). The specification, on para 374-376, contemplates a method for detecting colon cancer in a biological sample by quantifying the amount of expression or activity of colon cancer gene in a biological sample. The specification, on paragraph 118, teaches that gene GPR49 (G protein-coupled receptor 49) is an orphan-G protein coupled receptor with an unknown ligand and express in brain, skeletal muscle, placenta and spinal cord. The specification is silent on the levels of GPR49 expression in normal colon tissue. Based on the microarray data, application claims a method of diagnosing or monitoring colon cancer in a subject comprising detecting GPR49 protein in a biological sample of a subject. However, the specification neither teaches the levels of GPR49 protein in the colon cancer tissues compared to normal tissues, nor teaches a correlation between the levels of detected mRNA in microarray and levels of its coding protein in these tissues. The only statement or "evidence" showing the correlation between the levels of mRNA and protein of GPR49 colon cancer is the declaration filed on1/10/2007 by a co-inventor Dr. R. Dr. Martinez, who states that elevated levels of mRNA in colon cancer tissue compared to disease-free colon tissue would also have elevated amounts of the polypeptide encoded by that mRNA in colon cancer tissue, however, no data or other objective evidence was provided in the declaration.

The instant claims are drawn to a method of diagnosing or monitoring colon cancer in a subject comprising the step of detecting a level of a GPR49 polypeptide in a biological sample. In order to fulfill the requirements of 35 U.S.C. 101, said method must be indicative of a specific, substantial and credible utility. A substantial utility, by definition, is a utility that defines "real world" use, and a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility. In the instant case, the overexpressed mRNA expression associated colon cancer suggests a potential for diagnosis purpose, which, at the most, is an interesting invitation for further research and confirmation as it is not a practical method for "real world" use, and it requires significant further research and experimentation in order to form a useful and practical diagnosis method, which, by no means, is a routine or conventional experimentation. These further research and

experimentation, however, is part of the act of invention, and until it has been undertaken, the utility of claimed invention is not considered substantial.

> In *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), the Court held that:
> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. ... a patent is not a hunting license. ... [i]t is not a reward for the search, but compensation for its successful conclusion.

The art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide. For examples, the abstract of Brennan et al., (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teaches that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. The abstract of Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. The abstract of Powell et al., (Pharmacogenetics, 1998, Vol. 8, pp. 411-421) teaches that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. In this event although the mRNA of DNA 59610 was demonstrated to be overexpressed in uterine endometrial adenocarcinoma samples, according the teachings in the art, said demonstration cannot be relied upon to anticipate that the protein of SEQ ID NO: 6 would be similarly overexpressed in same cancer cells.

More evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels are following: The abstract of Hell et al., (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teaches that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. The abstract of Carrere et al., (Gut, 1999, vol. 44, pp. 545-551) teaches an absence of correlation between protein and mRNA levels for the Reg protein. The abstract of Guo et al., (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teaches that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both transcriptional and post-

translational level. These references serve to demonstrate that levels polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, the abstract of Jang et al., (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teaches that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Since there is not evidence showing the expression of protein or polypeptide GPR49 in colon or normal tissues, since the specification has not correlated the levels of GPR49 protein or polypeptide with the expression of mRNA, instant methods reciting diagnosing or monitoring colon cancer in a subject comprising the steps of detecting and comparing over expressed level of a GPR49 polypeptide and expression profile comprising GPR49 in biological samples do not meet the requirement of 35 U.S.C. 101.

If a molecule is to be used as a surrogate for a disease state some specific disease state must be identified in some way with the polynucleotide or polypeptide encoded therefrom. There must be some expression pattern or evidence of altered form that would allow the claimed polypeptides to be used in a diagnostic manner. However, in the absence of any disclosed relationship between the expression of protein and any disease or disorder, any information obtained in an effort to establish a differential expression pattern would constitute further research on establishing a specific, substantial, and credible utility for the method reliant on the presence of the GPR49 protein in cancer and normal colon tissue. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing". Therefore, without objective evidence that indicate differential expression of GPR49 protein in colon cancer tissue compared to normal colon tissue, the instant claims lack of specific, substantial, and credible asserted utility.

Claims 1, 2, and 5-7 remain and are again rejected under 35 U.S.C. 112, first paragraph as final office action dated 7/10/06. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

It is noted that one skilled in the art have recognized at time of invention filed that GPR49 gene is up-regulated in colon cancer (Gaitanaris et al., PG Pub 20006/0134109, Nakamura et al., PG Pub 2006/0111314, also see below, prior art record in conclusion). However, none of the publication has disclosed a method of diagnosing colon cancer by detecting a level of GPR49 protein in biological samples comprising tissue of a subject. Since applicant has not provided objective evidence to enable claimed method, one skilled in the art would be forced undo experimentation before practice claimed invention.

Response to applicant's argument

The response to the final office action filed 1/10/2007 has been carefully considered but is deemed not to be persuasive. Applicants, based on MPEP2164.01, argue that 1), absence of a working example is not a sufficient basis for rejection of the claims under the enablement; 2) lack of evidence not a sufficient basis for rejection of the claims under the enablement. In response to these arguments, the office considers that applicant left out the most important point for the enablement requirement of 35 USC112 first paragraph stated in this section of MPEP2164.01, "*The test of enablement is whether one reasonably skilled in the art could* ***make or use*** *the invention from the disclosure in the patent coupled with information know in the art without undue experimentation*". Instant claims recite a method of diagnosing or monitoring colon cancer comprising detecting and comparing a level of GPR49 polypeptide in a biological sample. However, the specification only provides a level of mRNA in the sample and no objective evidence to show the correlation of this protein with its coding mRNA and as discussed in rejection under the enablement (office action 7/10/06) "*one skilled in the art has not identified the association of the expression of GPR49 protein with normal or pathological condition comprising colon cancer*". Based on specification and information known in the art one reasonably skilled in the art could **NOT know how to make or use** claimed invention, a method of diagnosing or monitoring colon cancer

by detecting the a of a GPR49 polypetide. The reasons again are 1) no evidence showing the over expression of protein or polypeptide GPR49 in colon or normal tissues; 2) no correlated the levels of GPR49 polypeptide with the expression of mRNA; 3) the art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide.

Applicant further argues that over-expression of the gene provides at least a reasonable basis for concluding the difference in levels of GPR49 polypeptide exist and be useful in a method for diagnosing or monitoring colon cancer. Applicant also provides a declaration by Dr. Martinez, which includes an expert or inventor's opinion for the correlation of a level of mRNA with a protein. In response to this argument, the Office agree that over-expression of gene showing by mRNA provides at least a reasonable basis, however, objective evidence for a method of diagnosing or monitoring colon cancer by detecting a level of protein is not provided. Showing over-expressed mRNA colon cancer only provides a suggestion and a possibility for diagnosis purpose, which is at most an invitation for further research and confirmation. Regarding to the declaration by Dr. Martinez, the Office considers that the declaration is insufficient to overcome the rejection because the declaration only provides expert's opinion and irrelevant evidence for the exist of GPR49 polypeptide in those colon tissues (paragraph 5, using inducible promoters for gene expression, which is not shown as a promoter for GPR49 gene in colon tissues). The declaration does not provide factual evidence to support for the claimed method. See MPEP2164.05:

> "expert's opinion of the ultimate legal conclusion must supported by something more than a conclusory statement".
>
> "examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence".

Applicant also argues that the rejection of claim 7 that is not limited to the use of GPR49 polypeptides. The issue has been discussed at beginning of the action and again here: applicant originally elected group 17, a method for detecting polypeptide encoded by a colon cancer gene, GPR49 (SEQ ID NO: 84) for examination. Together with claims 1-6, the method of claim 7 has been examined for detecting the level of GPR49 polypeptides in colon samples. However, since the claim does not

specifically recite the method step detecting polypeptide or nucleic acid, it is also applicant's choice that claim could be drawn from further consideration for a non-elected invention if applicant interprets the method step comprising detecting a nucleic acid level of GPR49 gene. Applicant needs to affirm this issue in reply for this action. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained as reason of the record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, and 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 5-7 are vague and indefinite in the recitation of "GPR49" as the sole means of detecting and comparing the levels of polypeptide referred to in claim 1 and 7. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. This rejection can be obviated by amending the claims to specifically and uniquely identify GPR49, for example, by SEQ ID NO 84.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Afar et al., (US Patent Application Publication, No, 2003/0232350, priority to Nov, 29, 2001) disclose a method of diagnosing cancer including colon cancer by detecting the expression of genes including GPR49. Afar et al., disclose that the differential expression of the gene is comparison of cancer tissues to the normal or non-cancer tissues (paragraph 68 and 69). Afar et al., do not explicitly teach or suggest the protein level of GPR49 and over-expression of GPR49 polypeptide in the colon cancer tissue.

2. Gaithanaris et al., (US patent application publication, 2006/0134109, effective filing date Sep 9, 2002) disclose a method of diagnosing a disease comprising step of detecting expression of G-protein coupled receptor. Gaithanaris et al., suggest expression of GPCR gene comprising GPR49 determined by microarray (page 84 and page 101 table 16). Gaithanaris et al., do not teach or suggest a method of diagnosing colon cancer by detecting the level of GPR49 protein in the biological sample.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

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